

## IN THE TITLE

Amend the title as follows:

A system for increasing the production of [indole and quinoline alkaloids, particularly] camptothecins [and related compounds,] from plants

A system for increasing the production of camptothecins from plants

## IN THE SPECIFICATION:

In compliance with 37 C.F.R. § 1.121(b)(3), please amend the specification submitted on October 25, 2000 as noted hereinbelow. The substitute specification includes no new matter in compliance with 37 C.F.R. § 1.125(b). Also enclosed as Attachment "A" is a clean copy of the substitute specification.

**Amended Specification** (Page 3, Second Paragraph, Line 6-9):

B ( Many plant species which are known to produce camptothecins (the term camptothecins is used to describe camptothecin and its analogs [and other indole and quinoline alkaloids]). The plants which are known to produce camptothecins [camptothecin and its analogs] are:

### Guidance in the Specification:

Applicant respectfully disagrees that the specification provides no specific guidance regarding the effect of controlling other hormones on CPT production. The specification (Page 21, Lines 5-7) state: "Three plant hormones (auxins, cytokinins, and gibberellins) are known to promote and regulate the growth of a plant, and two plant hormones (abscisic acid and ethylene) are known to either inhibit plant growth or promote plant growth to maturity". The present invention selects auxin as the representative of the growth promoting hormones

and abscisic acid (ABA) as the growth inhibiting hormone to describe the effectiveness of alkaloid induction by the invented Trichome Management technique.

While Liu et al. (IDS reference #35) taught that there is a poor correlation between levels of ABA and CPT, the present invention provides a method for inducing ABA as a method to increase CPT concentration. Such method for induction of ABA includes applying water stress. As the specification states in example 3, "ABA begins forming when the plant senses an environment stress such as drought" (lines 12-13, page 22). Therefore, the applicant respectfully requests the present rejection be withdrawn.

**Predictability of the Art:**

Vincent et al. method (C-49) shows excessive amounts of variations of CPT yield within treatments. This unpredictability is largely caused by the problems in their motivation (i.e., no consideration of hormone levels), small sample size (i.e., 6 trees each treatment), and experimental design (i.e., no control for comparison). In contrast, with well-designed experiments with clear motivation (increasing both biomass growth and alkaloidal concentrations by controlling hormones) and large sample size (i.e., 69 plants each treatment for T-pruning), the present invention presents solid data of CPT yield variations with species or variety, tree age, seasonal change, tissue age, and different tissues. As a result, the claimed methods can produce at least 1,000 mg of stable CPT yield per plant annually. Several years of field trials in Texas are now leading the claimed invention for commercialization for CPT production.

**Amount of Experimentation Necessary:**

In addition to auxin as promoting hormones, the application also teaches the effects of growth inhibiting hormones (i.e., ABA) on CPT yield. Example 3 teaches CPT yield can be induced by inducing ABA through water stress (Figure 21).